Diseases of IMMUNITY
OBJECTIVES

• Differentiate between the concepts of “Innate” and “Adaptive” immunity
• Visually recognize and understand the basic roles of lymphocytes, macrophages, dendritic cells, NK cells
• Understand the roles of the major cytokines in immunity
• Differentiate and give examples of the four (4) different types of hypersensitivity reactions
OBJECTIVES

• Know the common features of autoimmune diseases, and the usual four (4) main features (Etiology, Pathogenesis, Morphology, and Clinical Expression) of Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjögrens, Systemic Sclerosis (Scleroderma), Mixed Connective Tissue Disease, and “Poly-” (aka, “Peri-”) - arteritis Nodosa

• Differentiate between Primary (Genetic) and Secondary (Acquired) Immunodeficiencies
OBJECTIVES

• Understand the usual four (4) main features of AIDS, i.e., etiology, pathogenesis, morphology, clinical expression
• Understand the usual four (4) main features of Amyloidosis
IMMUNITY

• INNATE (present before birth, “NATURAL”)

• ADAPTIVE (developed by exposure to pathogens, or in a broader sense, antigens)
MHC

Major Histocompatibility Complex

- A genetic “LOCUS” on Chromosome 6, which codes for cell surface compatibility
- Also called HLA (Human Leukocyte Antigens) in humans and H-2 in mice
- It’s major job is to make sure all self cell antigens are recognized and “tolerated”, because the general rule of the immune system is that all UN-recognized cells will NOT be tolerated
INNATE IMMUNITY

• BARRIERS
• CELLS: LYMPHOCYTES, MACROPHAGES, PLASMA CELLS, NK CELLS
• CYTOKINES/CHEMOKINES
• PLASMA PROTEINS: Complement, Coagulation Factors
• Toll-Like Receptors, TLR’s
ADAPTIVE IMMUNITY

• CELLULAR, i.e., direct cellular reactions to antigens

• HUMORAL, i.e., antibodies
CELLS of the IMMUNE SYSTEM

- LYMPHOCYTES, T - CD4 (helper), CD8 (cytotoxic)
- LYMPHOCYTES, B
- PLASMA CELLS (MODIFIED B CELLS)
- MACROPHAGES, aka “HISTIOCYTES”, (APCs, i.e., Antigen Presenting Cells)
- “DENDRITIC” CELLS (APCs, i.e., Antigen Presenting Cells)
- NK (NATURAL KILLER) CELLS
ANY ROUND CELL WITH RATHER DENSE STAINING CYTOPLASM AND MINIMAL CYTOPLASM IN CONNECTIVE TISSUE, A BIT BIGGER THAN AN RBC, IS A LYMPHOCYTE...UNTIL PROVEN OTHERWISE
MACROPHAGE
aka
HISTIOCYTE
MACROPHAGES are MONOCYTES that have come out of circulation and have gone into tissue.
MACROPHAGES, TEM, SEM
ANY CELL MIXED IN WITH LYMPHOCYTES BUT HAS A LARGER MORE “OPEN”, LESS DENSE, LESS CIRCULAR NUCLEUS WITH MORE CYTOPLASM IS A MACROPHAGE...

...UNTIL PROVEN OTHERWISE

ALMOST ALL “GRANULAR” or “PIGMENTED” CELLS IN CONNECTIVE TISSUE ARE MACROPHAGES. GRANULOMAS, GIANT CELLS, ARE CHIEFLY MACROPHAGES ALSO.
1) ROUND NUCLEUS
2) OVOID CYTOPLASM
3) PERIPHERAL CHROMATIN
4) “CLEAR ZONE” BETWEEN NUCLEUS AND WIDER LIP OF CYTOPLASM

PLASMA CELLS
DENDRITIC CELL
NK CELLS
GENERAL SCHEME of CELLULAR EVENTS

- APCs (Macrophages, Dendritic Cells)
- T-Cells → (Control Everything)
  - CD4 → “REGULATORS” (Helper)
  - CD8 → “EFFECTORS”
- B-Cells → Plasma Cells → AB’s
- NK Cells →
CYTOKINES

• MEDIATE INNATE (NATURAL) IMMUNITY, IL-1, TNF, INTERFERONS

• REGULATE LYMPHOCYTE GROWTH (many interleukins, ILs)

• ACTIVATE INFLAMMATORY CELLS

• STIMULATE HEMATOPOESIS, (CSFs, or Colony Stimulating Factors)
CYTOKINES/CHEMOKINES

• CYTOKINES are PROTEINS produced by MANY cells, but usually LYMPHOCYTES and MACROPHAGES, numerous roles in acute and chronic inflammation, AND immunity

—TNF, IL-1, by macrophages

• CHEMOKINES are small proteins which are attractants for PMNs
MHC

Major Histocompatibility Complex

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MHC MOLECULES  
(Gene Products)

• I (All nucleated cells and platelets), cell surface glycoproteins, ANTIGENS

• II (APC’s, i.e., macs and dendritics, lymphs), cell surface glycoproteins, ANTIGENS

• III Complement System Proteins
IMMUNE SYSTEM DISORDERS
WHAT CAN GO WRONG?

• HYPERSENSITIVITY REACTIONS, I-IV

• “AUTO”-IMMUNE DISEASES, aka “COLLAGEN” DISEASES (BAD TERM)

• IMMUNE DEFICIENCY SYNDROMES, IDS:
  – PRIMARY (GENETIC)
  – SECONDARY (ACQUIRED)
HYPERSENSITIVITY REACTIONS (4)

• I (Immediate Hypersensitivity)
• II (Antibody Mediated Hypersensitivity)
• III (Immune-Complex Mediated Hypersensitivity)
• IV (Cell-Mediated Hypersensitivity)
Type I IMMEDIATE HYPERSENSITIVITY

• “Immediate” means seconds to minutes
• “Immediate Allergic Reactions”, which may lead to anaphylaxis, shock, edema, dyspnea death
  – 1) Allergen exposure
  – 2) IMMEDIATE phase: MAST cell DEgranulation, vasodilatation, vascular leakage, smooth muscle spasm
  – 3) LATE phase (hours, days): Eosinophils, PMNs, T-Cells
TYPE II HYPERSENSITIVITY
ANTIBODY MEDIATED IMMUNITY

• ABs attach to cell surfaces
  – OPSONIZATION (basting the turkey)
  – PHAGOCYTOSIS
  – COMPLEMENT FIXATION (cascade of C1q, C1r, C1s, C2, **C3**, C4, C5.....)
  – LYSIS (destruction of cells by rupturing or breaking of the cell membrane)
TYPE II DISEASES

- Autoimmune Hemolytic Anemia, AHA
- Idiopathic Thrombocytopenic Purpura, ITP
- Goodpasture Syndrome (Nephritis and Lung hemorrhage)
- Rheumatic Fever
- Myasthenia Gravis
- Graves Disease
- Pernicious Anemia, PA
TYPE III HYPERSENSITIVITY
IMMUNE COMPLEX MEDIATED

• Antigen/Antibody “Complexes”
• Where do they go?
  – Kidney (Glomerular Basement Membrane)
  – Blood Vessels
  – Skin
  – Joints
• Common Type III Diseases- SLE (Lupus),
  Poly(Peri)arteritis Nodosa,
  Poststreptococcal Glomerulonephritis,
  Arthus reaction (hrs), Serum sickness (days)
TYPE IV HYPERSENSITIVITY
CELL-MEDIATED (T-CELL)
DELAYED HYPERSENSITIVITY

- Tuberculin Skin Reaction

- DIRECT ANTIGEN ➔ CELL CONTACT
  - GRANULOMA FORMATION
  - CONTACT DERMATITIS
SUMMARY

• I Acute allergic reaction

• II Antibodies directed against cell surfaces

• III Immune complexes

• IV Delayed Hypersensitivity, e.g., Tb skin test
RENAL TRANSPLANT REJECTION

- **HYPERACUTE** (minutes): AG/AB reaction of vascular endothelium
- **ACUTE** (days → months): cellular (INTERSTITIAL infiltrate) and humoral (VASCULITIS)
- **CHRONIC** (months): slow vascular fibrosis
AUTO-IMMUNE DISEASES

• Failure of SELF RECOGNITION
• Failure of SELF TOLERANCE
• TOLERANCE
  – CENTRAL (Death of self reactive lymphocytes)
  – PERIPHERAL (anergy, suppression by T-cells, deletion by apoptosis, sequestration (Ag masking))
• STRONG GENETIC PREDISPOSITION
• OFTEN RELATED TO OTHER AUTOIMMUNE DISEASES
• OFTEN TRIGGERED BY INFECTIONS
CLASSIC AUTOIMMUNE DISEASES (SYSTEMIC)

- **LUPUS** (SLE) Systemic Lupus Erythematosus
- RHEUMATOID ARTHRITIS
- SJÖGREN SYNDROME
- SYSTEMIC SCLEROSIS (scleroderma)
- “collagen” diseases (term no longer used)
CLASSIC AUTOIMMUNE DISEASES (LOCAL)

- HASHIMOTO THYROIDITIS
- AUTOIMMUNE HEMOLYTIC ANEMIA
- MULTIPLE SCLEROSIS
- AUTOIMMUNE ORCHITIS
- GOODPASTURE SYNDROME
- AUTOIMMUNE THROMBOCYTOPENIA
- “PERNICIOUS” ANEMIA
- INSULIN DEPENDENT DIABETES MELLITUS
- MYASTHENIA GRAVIS
- GRAVES DISEASE
N.B.

• The list of diseases proven to be “autoimmune” grows by leaps and bounds every year!!!
LUPUS (SLE)

- Etiology: Antibodies (ABs) directed against the patient’s own DNA, HISTONES, NON-histone RNA, and NUCLEOLUS
- Pathogenesis: Progressive DEPOSITION and INFLAMMATION to immune deposits, in skin, joints, kidneys, vessels, heart, CNS
- Morphology: “Butterfly” rash, skin deposits, glomerulonephritis (NOT discoid)
- Clinical expression: Progressive renal and vascular disease, POSITIVE A.N.A.
HOMOGENEOUS pattern

RIM pattern

SPECKLED pattern

NUCLEOLAR pattern
SLE, SKIN

SLE, GLOMERULUS
<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Prevalence in Patients, %</th>
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<tbody>
<tr>
<td>Hematologic</td>
<td>100</td>
</tr>
<tr>
<td>Arthritis</td>
<td>90</td>
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<tr>
<td>Skin</td>
<td>85</td>
</tr>
<tr>
<td>Fever</td>
<td>83</td>
</tr>
<tr>
<td>Fatigue</td>
<td>81</td>
</tr>
<tr>
<td>Weight loss</td>
<td>63</td>
</tr>
<tr>
<td>Renal</td>
<td>50</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>50</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>46</td>
</tr>
<tr>
<td>Myalgia</td>
<td>33</td>
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<tr>
<td>Pericarditis</td>
<td>25</td>
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<td>Gastrointestinal</td>
<td>21</td>
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<tr>
<td>Raynaud phenomenon</td>
<td>20</td>
</tr>
<tr>
<td>Ocular</td>
<td>15</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>14</td>
</tr>
</tbody>
</table>
MORE SYSTEMIC AUTOIMMUNE DISEASES

- RHEUMATOID ARTHRITIS
- SJÖGREN SYNDROME
- SCLERODERMA (SYSTEMIC SCLEROSIS)
NORMAL Bi-Layered Synovium

↑ Destructive Rheumatoid Synovitis

←NORMAL Bi-Layered Synovium
SJÖGREN SYNDROME
SCLERODERMA
(Systemic Sclerosis)
SYSTEMIC SCLEROSIS
(SCLERODERMA)
MORE AUTOIMMUNE DISEASES (LOCAL)

• HASHIMOTO THYROIDITIS
• AUTOIMMUNE HEMOLYTIC ANEMIA
• MULTIPLE SCLEROSIS
• AUTOIMMUNE ORCHITIS
• GOODPASTURE SYNDROME
• AUTOIMMUNE THROMBOCYTOPENIA (ITP)
• “PERNICIOUS” ANEMIA
• INSULIN DEPENDENT DIABETES MELLITUS (I)
• MYASTHENIA GRAVIS
• GRAVES DISEASE
IMMUNODEFICIENCIES

• PRIMARY (GENETIC)
• SECONDARY (ACQUIRED)
PRIMARY

- CHILDREN with repeated, often severe infections, cellular AND/OR humoral immunity problems, autoimmune defects
- BRUTON (X-linked agammaglobulinemia)
- COMMON VARIABLE
- IgA deficiency
- Hyper IgM
- DI GEORGE (THYMIC HYPOPLASIA) 22q11.2
- SCID (Severe Combined Immuno Deficiency)
- ….with thrombocytopenia and eczema (WISKOTT-ALDRICH)
- COMPLEMENT DEFICIENCIES
ADA = ADENOSINE DEAMINASE
# Examples of Infections in Immunodeficiencies

<table>
<thead>
<tr>
<th>Pathogen Type</th>
<th>T-Cell-Defect</th>
<th>B-Cell Defect</th>
<th>Granulocyte Defect</th>
<th>Complement Defect</th>
</tr>
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<tbody>
<tr>
<td>Bacteria</td>
<td>Bacterial sepsis</td>
<td>Streptococci, staphylococci, <em>Haemophilus</em></td>
<td>Staphylococci, <em>Pseudomonas</em></td>
<td>Neisserial infections, other pyogenic bacterial infections</td>
</tr>
<tr>
<td>Viruses</td>
<td>Cytomegalovirus, Epstein-Barr virus, severe varicella, chronic infections with respiratory and intestinal viruses</td>
<td>Enteroviral encephalitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungi and parasites</td>
<td><em>Candida, Pneumocystis</em> <em>carinii</em></td>
<td>Severe intestinal giardiasis</td>
<td><em>Candida, Nocardia, Aspergillus</em></td>
<td></td>
</tr>
<tr>
<td>Special features</td>
<td>Aggressive disease with opportunistic pathogens, failure to clear infections</td>
<td>Recurrent sinopulmonary infections, sepsis, chronic meningitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AIDS

(SECONDARY IDS)

- **Etiology**: HIV
- **Pathogenesis**: Infection, Latency, Progressive T-Cell loss
- **Morphology**:

  - **Clinical Expressions**: Infections, Neoplasms, Progressive Immune Failure, Death, HIV+, HIV-RNA (Viral Load)
EPIDEMIOLOGY

- HOMOSEXUAL (40%, and declining)
- INTRAVENOUS DRUG USAGE (25%)
- HETEROSEXUAL SEX (10% and rising)
ETIOLOGY
PATHOGENESIS

ATTACHING  BUDDING
PATHOGENESIS

EARLY BUDDING
PATHOGENESIS

LATE BUDDING
PATHOGENESIS

MATURE NEW VIRIONS
REVERSE TRANSCRIPTASE

- The enzyme reverse transcriptase (RT) is used by retroviruses to transcribe their single-stranded RNA genome into single-stranded DNA and to subsequently construct a complementary strand of DNA, providing a DNA double helix capable of integration into host cell chromosomes.
PATHOGENESIS
PATHOGENESIS

1) PRIMARY INFECTION
2) LYMPHOID INFECTION
3) ACUTE SYNDROME
4) IMMUNE RESPONSE
5) LATENCY
6) AIDS
GENERAL IMMUNE ABNORMALITIES

• LYMPHOPENIA
• DECREASED T-CELL FUNCTION
• B-CELL ACTIVATION, POLYCLONAL
• ALTERED MONOCYTE/MACROPHAGE FUNCTION
INFECTIONS

- Protozoal/Helminthic: Cryptosporidium, PCP (Pneumocystis Carinii Pneumonia), Toxoplasmosis
- Fungal: Candida, and the usual 3
- Bacterial: TB, Nocardia, Salmonella
- Viral: CMV, HSV, VZ
CRYPTOSPORIDIUM
CASEATING GRANULOMA
CANCERS of AIDS

• KAPOSI SARCOMA
• B-CELL LYMPHOMAS
• CNS LYMPHOMAS
• CERVIX CANCER, SQUAMOUS CELL
AMYLOIDOSIS

• BUILDUP OF AMYLOID “PROTEIN”
  – AL (Amyloid Light Chain)
  – AA (NON-immunoglobulin protein)
  – Aβ (Alzheimer’s)

• WHERE? BLOOD VESSEL WALLS, at first
  – KIDNEY
  – SPLEEN
  – LIVER
  – HEART
CONGO RED STAIN, WITHOUT, and WITH, POLARIZATION
AMYLOID ASSOCIATIONS

• PLASMA CELL “DYSCRASIAS”, i.e., MULTIPLE MYELOMA
• CHRONIC GRANULOMATOUS DISEASE, e.g., TB
• HEMODIALYSIS
• HEREDOFAMILIAL
• LOCALIZED
• ENDOCRINE MEAs (Multiple Endocrine Adenomas)
• AGING